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STABILIZATION OF A NEW ANTIULCER DRUG (LANSOPRAZOLE) IN THE SOLID DOSAGE FORMS

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SUMMARY

In the previous study, we clarified that enteric granules were appropriate dosage forms of lansoprazole. The establishment of these formulations, however, was difficult because some of the excipients needed for these formulations are incompatible with the drug. We examined the effects of adding magnesium carbonate as an alkaline stabilizer and could get stable enteric granules. We also discuss the mechanism of stabilization.

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INTRODUCTION

In the previous study[1], we clarified that the development of an enteric dosage form of lansoprazole was necessary to protect against degradation in the stomach. Generally, enteric granules have better absorption properties than an enteric tablet from the standpoint of gastric emptying[2-6].

Therefore, enteric granule formulations were developed. The establishment of these formulations, however, was difficult because some of the excipients needed for these formulations are very incompatible with the drug.

In this study, we examined stabilizers, the mechanism of stabilization of lansoprazole in enteric granules.

EXPERIMENTAL METHODS

1. Materials and reagents

Lansoprazole was synthesized at Takeda Chemical Industries, Ltd. Excipients used in the dosage forms are specified in the Pharmacopoeia of Japan (JP) or Standards for Ingredients of Drugs not in the JP.

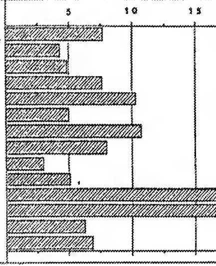
Triethylamine and phosphoric acid were of reagent grade, and methanol was of analytical grade from Wako Pure Chemical Ind.,Ltd.

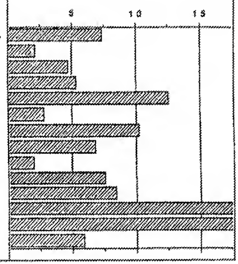
2. Assay of lansoprazole in dosage forms

To weighed sample of pulverized dosage form was added 40ml of methanol followed by sonication for 5 minutes, and to the methanol solution was added 5ml of the internal standard (40mg/ml of buthyl paraoxybenzoate in methanol) and 5ml of methanol. To 1ml of the solution filtered with a membrane filter (0.45 μ m) was added 9ml of distilled water. This solution was assayed by high performance liquid chromatography (HPLC) under the conditions shown in Table 1 in comparison with similarly prepared reference standards.

TABLE 3
Compatibility studies of lansoprazole with excipients

Excipients	Ratio	60° 1W % of Initial	60° 1W ΔE	40°, 75% RH 1W % of Initial	40°, 75% RH 1W ΔE
None	1:0	99.6%		99.1%	
Lactose	1:5	98.9		99.2	
Sucrose	1:5	99.6		99.2	
Corn Starch	1:5	99.6		99.4	
Avicel	1:5	99.2		99.7	
L-HPC	1:5	99.2		98.3	
CMC-Ca	1:5	99.0		98.2	
HPC	1:5	98.5		99.8	
Titanium Oxide	1:5	99.3		98.6	
HPMC	1:5	99.1		99.6	
PEG-6000	1:5	60.3		99.0	
Pluronic F68	1:5	41.3		80.0	
PVP	1:5	91.5		57.2	
Mg-St	20:1	99.6		99.4	





Avicel ; crystalline cellulose
L-HPC ; low substituted hydroxypropylcellulose
ECG-505 ; carboxymethylcellulose calcium
HPC-L ; hydroxypropylcellulose
TC-5 ; hydroxypropylmethylcellulose 2910
Pluronic F68 ; polyoxyethylene(160) polyoxypropylene(30) glycol
PVP ; polyvinylpyrrolidone
Mg-St ; magnesium stearate

TABLE 4
Fundamental formulations for screening of stabilizers

Drug	Lansoprazole	30mg(15%)
Diluent	Lactose	26mg(13%)
Diluent	Corn starch	80mg(40%)
Spheronizer	Crystalline cellulose	20mg(10%)
Disintegrant	Carboxymethylcellulose calcium	10mg(5%)
Binder	Hydroxypropylcellulose	10mg(5%)
Lubricant	Macrogol 6000	4mg(2%)
Stabilizer	?	20mg(10%)
	(H_2O)	100 μ l
Total		200mg

Table 3 shows the results (the percent of initial and the discoloration) of the compatibility experiments with some excipients needed for solid dosage forms. Some excipients are incompatible with lansoprazole.

In the previous paper[1], we clarified that the development of an enteric dosage form was necessary to protect against degradation in the stomach. Generally, enteric granules have better absorption properties than an enteric tablet from the standpoint of gastric emptying[2-5].

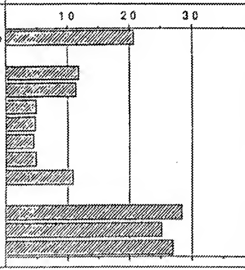
Therefore, enteric granule formulations were developed. The establishment of these formulations, however, was difficult because some of the excipients needed for these formulations manufactured by an extrusion granulation method (for example macrogol 6000, crystalline cellulose, carboxymethylcellulose calcium etc.) are incompatible with the drug as shown in Table 3. It was then suggested that the addition of a stabilizer is necessary.

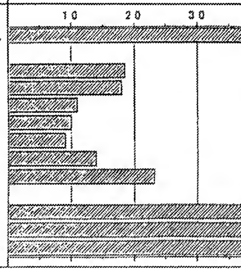
2. Screening of stabilizers

Some excipients described above are necessary when enteric granules are manufactured by an extrusion granulation method. Therefore, stabilizers were screened using the fundamental formulations shown in Table 4.

TABLE 5
Screening of stabilizers for lansoprazole granules

Stabilizer	after drying at 40° for 16 hours		40°/75% RH 4W		pH*
	% of Initial	ΔE	% of Initial	ΔE	
None	100.0 %		60.2 %		5.3
Potassium Carbonate	100.5		89.0		11.2
Sodium Carbonate	100.4		90.1		11.1
Magnesium Oxide	100.6		94.7		9.3
Magnesium Hydroxide	100.8		94.8		9.2
Magnesium Carbonate	100.5		95.0		9.1
Calcium Caobonate	100.9		94.0		9.0
Sodium Bicarbonate	100.9		88.1		8.3
Magnesium Sulfate	88.2		50.3		4.9
Magnesium Chloride	84.4		48.5		4.8
Calcium Chloride	75.3		45.6		4.8





*; pH of 1% Solution or Suspension

It was suggested that lansoprazole is degraded when a proton attacks the sulfoxide in the structure[9-11]. Mainly alkaline substances were screened as stabilizers. The mass after drying at 40° for 16 hours was discolored without a stabilizer. Table 5 shows the results of the stabilizer screening which examined the percent of initial content and the discoloration after drying at 40° for 16 hours and after being stored at 40°/75% RH for 4 weeks. Table 5 also shows the pH of a 1% aqueous solution or suspension of the substances screened.

Stabilizing effects were obtained by adding alkaline substances which suppressed the attack by protons, but stronger alkaline substances do not necessarily provide better stabilization, that is, magnesium carbonate or calcium carbonate (pH 9) show stronger stabilization effects than sodium bicarbonate (pH 8), sodium carbonate or potassium carbonate (pH 11). Therefore, the mechanism of stabilization is not merely suppression of the attack by protons. Neutral or acidic substances did not stabilize the compound.

From these results, it was suggested that a suitable pH region exists for stabilization.

3. Mechanism of stabilization

Since it was suggested that a suitable pH region exists for stabilization, we examined the relationship between pH and the degradation rate constants in solution (Fig.1) and that between pH and the solubility (Fig.2).

Fig.1 shows that increasing pH results in better stability based on the negative correlation between pH and the degradation rate constants. Generally, total solubility (S) of weak electrolytes is generally expressed as the sum of S_1 (saturated solubility of undissociated compound) and S_2 (solubility of dissociated compound)[12]. Fig.2 shows that the solubility of lansoprazole is constant below pH 9 and that increasing pH above pH 9 results in increased solubility.

Lansoprazole is unstable especially under high humidity conditions. The reason for this is hypothesized to be as follows

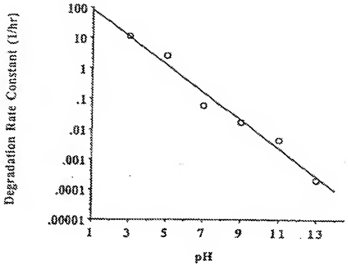


FIGURE 1.
Relationship between pH and the degradation rate constant of lansoprazole

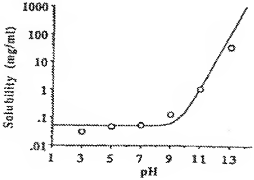


FIGURE 2.
Relationship between pH and the solubility of lansoprazole

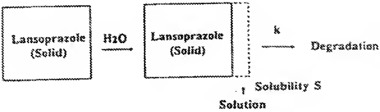


FIGURE 3.
Degradation of lansoprazole in the solid state

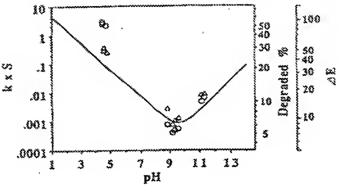


FIGURE 4.
Relationship between pH and (k x S) for lansoprazole
———— , calculated; ○, degraded %; △, ⊿E

(Fig.3). If a little of water exists, part of lansoprazole dissolves. The degradation content of lansoprazole would be proportioned to the product of the degradation rate constant (k) and the total solubility (S) as described in equation (1).

$$-\frac{d(\text{Lansoprazole})}{dt} \propto k \times S \qquad \text{(1)}$$

As shown in Fig.4, the relationship between pH and (k x S) for lansoprazole is expressed as a curve with the minimum at pH 9. The degradation contents and the discoloration of lansoprazole after

storage at 40° /75% RH for 4 weeks shown in Table 5 correctly fit the curve shown in Fig.4. Therefore, it is suggested that the hypothesis shown in Fig.3 is appropriate. From the results, the mechanism of stabilization of lansoprazole in dosage forms appears to be that the environment of dosage forms becomes pH 9 at which the degradation of lansoprazole is minimum.

It was therefore suggested that the best stabilizer should be magnesium carbonate : the pH of a saturated solution is pH 9.1.

CONCLUSIONS

Enteric granule formulations for lansoprazole were developed since enteric granules generally have better absorption properties than an enteric tablet from the standpoint of gastric emptying. The establishment of these formulations, however, was difficult because some of the excipients needed for these formulations are incompatible with the drug. We examined the effects of adding magnesium carbonate as an alkaline stabilizer and could get stable enteric granules. We also examined the mechanism of stabilization of lansoprazole in dosage forms, and it was suggested that the environment of dosage forms becomes pH 9 at which the degradation of lansoprazole is minimum.

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